UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,390	04/16/2002	Wolfgang Christian Hans	DCKQ:002	2253

7590 07/15/2005

Patricia A Kammerer
Howrey Simon Arnold & White
750 Bering Drive
Houston, TX 77057-2198

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,390	HANS ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11,19-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,19-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *122004*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

1) A request for continued 01/10/05 examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 01/10/05 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 01/10/05 and 05/02/05 in response to the final Office Action mailed 10/06/04. The amendment filed 05/02/05 is compliant.

Status of Claims

3) Claim 25 has been canceled via the amendment filed 05/02/05.

Claims 10, 11, 24, 26, 28 and 29 have been amended via the amendment filed 05/02/05.

Claims 10, 11, 19-24 and 26-29 are pending and are under examination.

The Steidler Declaration

4) Acknowledgment is made Applicants' submission of the Steidler declaration filed 01/10/05. The declaration has been fully considered. See paragraph 13 below.

Rejection(s) Moot

5) The rejection of claim 25 made in paragraph 12 of the Office Action mailed 11/26/03 and maintained in paragraph 14 of the Office Action mailed 10/06/04 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 - Applicants' IDS) and Malin *et al.* (*Ann. Nutr. Metabol.* 40: 137-145, 1996) in view of Steidler *et al.* (WO 97/14806 - Applicants' IDS), is moot in light of Applicants' cancellation of the claim.

6) The rejection of claim 25 made in paragraph 13 of the Office Action mailed 11/26/03 and maintained in paragraph 15 of the Office Action mailed 10/06/04 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 – Applicants' IDS) in view of Le Page *et al.* (WO 93/17117), Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993) (Wells *et al.*, June, 1993), and Wells *et al.* (*Appl. Environ. Microbiol.* 59: 3954-3959, November 1993) (Wells *et al.*, November, 1993), is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 25 made in paragraph 17(a) of the Office Action mailed 10/06/04 under 35 U.S.C. § 112, second paragraph as being indefinite, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

8) The rejection of claims 10, 11, 19-21, 23-24 and 27 made in paragraph 12 of the Office Action mailed 11/26/03 03 and maintained in paragraph 14 of the Office Action mailed 10/06/04 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 - Applicants' IDS) and Malin *et al.* (*Ann. Nutr. Metabol.* 40: 137-145, 1996) in view of Steidler *et al.* (WO 97/14806 - Applicants' IDS), is withdrawn upon further consideration.

9) The rejection of claims 10, 11, 19-24 and 27 made in paragraph 13 of the Office Action mailed 11/26/03 and maintained in paragraph 15 of the Office Action mailed 10/06/04 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 – Applicants' IDS) in view of Le Page *et al.* (WO 93/17117), Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993) (Wells *et al.*, June, 1993), and Wells *et al.* (*Appl. Environ. Microbiol.* 59: 3954-3959, November 1993) (Wells *et al.*, November, 1993), is withdrawn in light of Applicants' amendments to the claims and/or the base claim. A modified rejection is made below to reject the claims as amended.

10) The rejection of claim 26 made in paragraph 14 of the Office Action mailed 11/26/03 and maintained in paragraph 15 of the Office Action mailed 10/06/04 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 - Applicants' IDS) as modified by Malin *et al.* (*Ann. Nutr. Metabol.* 40: 137-145, 1996) and Steidler *et al.* (WO 97/14806 - Applicants' IDS) as applied to claim 10, and further in view of Silk (WO 8203329), is withdrawn. A modified rejection is made below.

11) The rejection of claim 28 made in paragraph 17(b) of the Office Action mailed 10/06/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

12) Claims 10, 11, 19-24 and 26-29 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicant(s) regards as the invention.

(a) Claim 10 is vague and indefinite in the recitation: 'the oral administration of a recombinant microorganism ..... *in vivo*', because it is unclear to whom or what subject the recombinant microorganism is administered to.

(b) Claim 19 is vague and indefinite in the recitation: 'the microorganism is a bacterial strain', because while it is known in the art that --a bacterium-- is included within the genus of 'microorganism', a 'strain' is not.

(c) Claim 20 is vague, indefinite and/or incorrect in the limitation: 'of claim 19, wherein the microorganism is a ..... bacterial strain'. Since the microorganism of claim 19 is already limited to 'a bacterial strain', the recitation 'the microorganism' in the dependent claim 20 is not properly further limiting.

(d) Claim 21 lacks proper antecedence in the limitation: 'the bacterial strain'. Claim 21 depends from claim 20, which recites 'a ... gram-positive bacterial strain'.

(e) Claim 22 is vague, indefinite and/or incorrect in the limitation: 'of claim 21, wherein the bacterial strain is a *Lactococcus lactis*'. Since the bacterial strain of claim 21 is already limited to 'a *Lactococcus* species', the recitation 'the bacterial strain' in the dependent claim 22 is not properly further limiting. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --of claim 21, wherein the *Lactococcus* species is *Lactococcus lactis*--.

(f) Claim 28 is vague and indefinite in the language: 'a nucleotide sequence represented by ..... SEQ ID NO: 1, 2 or 3', because it is unclear whether or not the limitation 'represented by' is intended to be closed or open claim language. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --the nucleotide sequence of SEQ ID NO: 1, 2 or 3--.

(g) Claims 11, 19-24 and 26-29, which depend directly or indirectly from claim 10, are also rejected as being indefinite, because of the indefiniteness identified above in the base claim.

Response to Applicants' Arguments on Art Rejections

13) With regard to the art rejections, Applicants present the following arguments.

(a) For a combination of references to render a claim obvious, there must be a suggestion or motivation to combine reference teachings, a reasonable expectation of success, and the references must teach all of the claim limitations, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

(b) Podolsky determined that trefoil peptides are naturally expressed in great abundance at the mucosal surface of the gastrointestinal tract, and are in fact expressed to a significantly greater extent in the proximity of the injured bowel. Podolsky further demonstrates (page 28) that trefoil-deficient mice that are treated with DSS (dextran sulfate sodium) develop severe colonic erosions. One of skill in the art might likely conclude, as recognized by the Examiner and acknowledged by Applicants in the present specification (see paragraph 0071) that trefoil peptides would likely be useful for treating intestinal disorders such as colonic diseases. However, the mere recognition that trefoil peptides might be useful for treating intestinal disorders is not sufficient to render obvious a particular delivery means of treating intestinal disorders. One of skill in the art recognizes that a reasonable expectation of successful pharmacological treatment depends on having a delivery method that is compatible both with the pharmacological agent that is to be delivered and with the target organ/area to which it is to be delivered. Podolsky does not teach any method of treatment by any means of delivery, so one of skill in the art would have to look beyond Podolsky to derive at a method of treating intestinal disorders. Apparently, the Examiner recognized this fact and has searched for additional art to construct a 35 U.S.C. 103 rejection, rather than rejecting the claims under 35 U.S.C. 102.

(c) Steidler describes that bacteria, such as *Lactobacteria*, can be used to deliver/ administer bioactive proteins *in situ*. While Steidler does teach a delivery method for pharmacologically active proteins, there are many delivery methods known in the art. Steidler does not suggest that its method would be particularly suited for delivering trefoil peptides to the intestines. As the Examiner recognized, if Steidler did teach delivering trefoil peptides to the intestine to treat intestinal disorders, then Steidler would have been a 102 reference. Because Steidler is a 103 reference, the relevant question is whether one of skill in the art would be motivated to combine Steidler with Podolsky, with a reasonable expectation of success, to derive the instantly claimed method. Answering this question requires one to evaluate all of the art that one of

skill in the art would consider at the time the invention was made. As shown below, the state of the art when the invention was made would not suggest a reasonable expectation of success for arriving at the presently claimed method. Based on the state of the at the time the invention was made, one of skill in the art would not have expected the oral administration of a recombinant microorganism expressing a trefoil peptide *in vivo* to be successful for treating intestinal disorders.

(d) Poulsen *et al.* (*Gut*, 1999, vol. 45, pp. 516-522) compared oral and systemic PTFF2 with respect to the healing of gastric and duodenal ulcerations, and detailed the metabolism and distribution of the peptides in the gastrointestinal tract. While some benefit was observed in the upper gastrointestinal tract, no beneficial effect appeared in the colon. As specifically stated by Poulsen, the fact that parenteral trefoil factor 2 binds to the mucus layer of the intestine and is apparently fermented and degraded in the caecum by bacteria 'suggests that a beneficial effect of orally administered TFF2 in the colon is unlikely" (page, 517 and page 522, lines 1 1-13). In fact, duodenal ulceration was aggravated by orally administered trefoil protein. See, page 519, lines 37-44. These findings explicitly show that the suggestion of Podolsky does not appear to work in the intestine, especially below the caecum in regions such as the colon. Applicants urge that it is not speculation that 24 hours after oral administration, only 6 % of radio labeled 125l-pTFF2 is left in the gastrointestinal tract, whereas 52 % is present in the urine and 27 % in the thyroid. The question to be asked is whether one of skill in the art would be motivated, in light of the state of the art, to invest the time, effort, and money on a quest that published data suggests is not reasonably likely to succeed. Furthermore, Applicants demonstrated in their disclosure that mice having Dss-induced colonic inflammation responded favorably when treated according to the present invention, i.e., orally with a recombinant microorganism expressing a trefoil peptide *in vivo* (in this case TFFI), whereas mice treated orally with purified TFFI, did not respond to treatment. Applicants allege that in dismissing Applicants' showing, the Office failed to offer any supporting documentary evidence.

(e) Neither Playford nor Chinery actually shows that trefoil proteins are effective for treating intestinal disorders via any delivery method. Applicants acknowledge that Playford demonstrates that transgenic mice that overexpress human pS2 trefoil peptide have increased resistance to intestinal damage, and Chinery shows that trefoil peptides protect against stomach ulcers. Applicants state that neither Playford nor Chinery actually tried to treat intestinal disorders with trefoil proteins. Weighing the fact that neither Playford nor Chinery teach anything about the

robustness of trefoil peptides in the intestine or the treatment of intestinal disorders by providing trefoil peptides, against the fact that Poulsen presents data that TFF2 does not survive long in the colon and Applicants own data demonstrates that purified TFFI is ineffective for treating colitis, one of skill in the art would conclude that there would not be a reasonable expectation of success such as to render the instantly claimed method obvious. The Examiner has not cited any suggestion in the prior art that intestinal disorders have been successfully treated by orally delivering a trefoil peptide to the intestine by any delivery means. Rather, the art, and Applicants' own experimentation, suggest that doing so would be unsuccessful. The most that the art suggested was that trefoil proteins are related to gastrointestinal inflammation.

(f) The results provided by the presently claimed invention are quite surprising and unexpected. In view of the state of the art at the time the invention was made, one of skill in the art would have expected that if they used a recombinant bacteria as per Steidler to orally deliver the trefoil peptides of Podolsky to treat intestinal disorders, the trefoil peptides would simply stick to the mucus in the gut and be degraded, as taught by Poulsen. Surprisingly, this does not happen. Applicants have conducted further experiments and can now explain why the present method of delivering trefoil peptides succeeds, where one of skill in the art would have expected to fail, based on the state of the art at the time the invention was made. A previously unknown property of a recombinant microorganism expressing a trefoil peptide *in vivo* allows the microorganism to penetrate through the mucus layer and intercalate among the cells in the intestine and thereby express the peptide so that it can be taken up by the cell and not be degraded. This is a property of the bacterium itself and is not a result of the fact that the bacterium expresses TFF.

(g) Applicants submit a 132 Declaration by inventor Lothar Steidler. The declaration provides data obtained with a culture of lL-10-producing *Lactococcus lactis* and control *L. lactis* which were inoculated into isolated murine intestinal loops and the loops dissected and histologically processed. The data are said to show penetration of *L. lactis* in between the cells of the intestinal tissue. Applicants conclude that: (a) This is why 'bacteria-produced protein' has a beneficial effect on inflammation in the intestine, whereas purified protein simply sticks in the mucus and is ineffective; (b) This mode of action could not have been foreseen at the time the invention was made; (c) One of skill in the art would not have expected bacteria-produced protein

to be any more effective than purified protein; and (d) The benefits of the present invention are only understood with the hindsight knowledge of Applicants' disclosure.

In sum, Applicants contend that: (a) Podolsky suggests only that trefoil proteins would likely be useful for treating intestinal disorders such as colonic diseases; (b) Podolsky does not suggest any means of delivering such proteins in a way that one of skill in the art would expect to be effective, based on the state of the art when the invention was made; (c) La Page and the Wells articles do not teach any delivery means that one of skill in the art would expect to be successful, given the state of the art at the time the invention was made. Specifically, these articles do not suggest any delivery means that would be expected to overcome the known barriers to treating intestinal disorders with trefoil proteins.

Applicants' arguments have been carefully considered, but are not persuasive. Both a suggestion or motivation to combine reference teachings and a reasonable expectation of success have been established below under the art rejections. The references cited therein do teach all of the claim limitations.

First, it is important to note what 'the time of the invention' is in the instant case. The effective filing of the instant application is July 1999, and the publication date of Poulsen *et al.* is well after this effective filing data, i.e., October 1999. The WIPO publication of Podolsky, WO 97/38712, was published in October 1997. The effective filing date of the currently cited Podolsky (US 6,221,840) is at least April 1996. Therefore, at the time of the effective filing date of the instant application, the teachings of Poulsen *et al.* were not available. Instead, at the time of the instant invention what was known to those of skill in the pertinent art was what was disclosed by Podolsky; Jorgensen *et al* (*Regulatory Peptides* 3: 231, 1982); and the May 1999 reference of Tran *et al.* (*Gut* 44: 636-642, May 1999). Contrary to Applicants' assertion and as explained herebelow and under the art rejection (see paragraph 14 below), well before the publication of Poulsen *et al.* in October 1999 and well before Applicants' showing of supposed lack of response in mice treated orally with purified TFF1, Podolsky (WO 97/38712 and US 6,221,840) contemplated and disclosed a method of treating intestinal lesion in a patient comprising oral administration of a therapeutic composition comprising an intestinal trefoil factor. See the patented claims of Podolsky ('840), claims 2, 7 and 16 in particular. Additionally, at lines 13-21 in column 1, Podolsky ('840) reflected the state of the art at the time of the effective filing date of the Podolsky patent. Podolsky ('840) discussed about

Jorgensen's (*Regulatory Peptides* 3: 231, 1982) showing that a pancreatic spasmolytic peptide inhibited gastrointestinal motility and gastric acid secretion in laboratory animals after oral administration, and Jorgensen's suggestion about the potential utility for the peptide in the treatment of gastrointestinal ulcer diseases in man.

In addition to Podolsky's and Jorgensen's disclosure on oral administration of a trefoil peptide for therapeutic purposes, Tran *et al.* provided teachings that are contrary to Poulsen's alleged non-motivational teachings. In May 1999, i.e., about a couple months before the effective filing date of the instant application, Tran *et al.* (*Gut* 44: 636-642, May 1999) used an art-established model of colitis that exhibits damage and repair profiles in common with the human inflammatory bowel diseases, ulcerative colitis and Crohn's disease, and expressly demonstrated that exogenously administered trefoil peptide induces therapeutic effects, i.e., promotion of rapid repair of the epithelium and reduction in inflammatory indexes. Tran *et al.* demonstrated that the trefoil peptide TEF2 potently accelerated healing and reduced inflammation in a rat model of colitis. Tran *et al.* showed that human TEF2 enhanced the rate of colonic epithelial repair and reduced local inflammation in a rat model of colitis suggesting that luminal application of trefoil peptides have therapeutic potential in the treatment of inflammatory bowel disease. Tran *et al.* further taught that trefoil peptides reduce the symptoms of colitis by multiple mechanisms (see title; abstract; paragraph bridging left and right columns on page 641; and right column on page 641). Thus, at the time of the instant invention and well before Poulsen *et al.* published their study, at least the disclosure Podolsky and the teachings of Jorgensen *et al.* and Tran *et al.* documented that trefoil peptides were already used in the treatment of intestinal disorders, Crohn's disease or colitis. Thus, contrary to Applicants' arguments and irrespective of what the reasons might be for Applicants' lack of success with the orally administered purified trefoil peptide in mice, at the time of the instant invention, there was ample motivation for one of skill in the art to provide an active local source of trefoil peptide via a recombinant microorganism expressing such a peptide, which microorganism would be expected to continue producing the trefoil peptide locally at the site of the lesions. Furthermore, Podolsky's, Trans' and Jorgensen's teachings also indicate that the administered trefoil peptide did not get degraded, did not stick to mucus, or induced therapeutic effects despite sticking to the mucus. The fact that trefoil peptide is naturally co-produced with mucus and

upregulated during the repair phase following ulceration and IBD (see page 636 of Tran *et al*, May 1999) appears to be indicative of its cytoprotective action even in a mucousy environment. Thus, there was both motivation as well as reasonable expectation of success at the time of the invention.

The teachings of Chinery *et al.* (*Clin. Sci.* 88: 401-403, 1995) and Playford *et al.* (*PNAS* 93: 2137-2142, March 1996) have been made of record previously. Contrary to Applicants' assertion, one would not and could not have weighed Playford's or Chinery's teachings with those of Poulsen *et al.* 'at the time of the invention' since Poulsen's teachings were not available at the time of the effective filing date of the instant invention. Instead, one would have weighed Playford's or Chinery's teachings with those of Podolsky to reasonably arrive at the instant invention.

The state of the art at the time of the invention suggests that those of skill in the art had already used recombinant lactobacteria, including *Lactococcus lactis,* expressing a heterologous polypeptide antigen intracellularly or on the cell surface, by oral administration for the successful delivery of the polypeptide antigen to the desired site in the GI tract wherein the heterologous antigen brought about a response beneficial to the host. See below the teachings of Le Page *et al.* (US 6,221,648) and Steidler *et al.* (US 6,605,286) as well as the teachings of Robinson *et al. Nature Biotechnol.* 15: 653-657, 1997 (see title; Figures 4 and 5; and pages 655 and 656); Pouwels *et al. J. Biotechnol.* 44: 183-192, 1992 (see title; abstract; and Discussion); and Pouwels *et al. Int. J. Food Microbiol.* 41: 155-167, 1998 (see sections 2, 7, 7.2 and 8). There appears to be no indication in the state of the art at the time of the invention that the polypeptide antigen expressed by these recombinant lactobacteria, on oral administration of these lactobacteria, got degraded or stuck to the mucus such that the expressed polypeptide failed to induce the expected beneficial effect, i.e., therapeutic or prophylactic effect. Therefore, as set forth below in paragraph 14, given Podolsky's express teaching that trefoil peptides are 'not degraded within the digestive tract' and Podolsky's express teaching that trefoil peptides are orally administered for treating intestinal lesions in a patient, one of skill in the art would have reasonably expected La Page's, Wells' (June, 1993) or Steidler's recombinant *Lactococcus lactis* expressing Podolsky's trefoil peptide to successfully deliver the peptide to the site of lesions on oral administration. What are characterized by Applicants as unexpected surprising results do not appear to be unexpected since those of skill in the art had already successfully used recombinant *Lactococcus lactis* expressing a biologically active heterologous antigen intracellularly or on the cell surface, for delivery of the antigen by oral

administration.

With regard to the rejection of claim 26 and the teachings of Silk, Applicants have not advanced any substantive arguments other than stating that one of skill in the art would not expect that using a gastric catheter, as per Silk, would overcome the recognized barriers to using trefoil peptides for treating intestinal disorders.

In sum, one cannot show non-obviousness by attacking references individually where the rejections are based on combination(s) of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the claimed method is obvious over the prior-art method, given the teaching of the applied prior art. As explained above, the invention as a whole, would have been *prima facie* obvious to a practitioner in view of the knowledge in the art at the time of invention, the state of the art at the time of the invention, and the combined teachings of Podolsky, Le Page *et al.*, Wells *et al.* (June, 1993), Steidler *et al.* and Tran *et al.* It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

Rejection(s) under 35 U.S.C § 103

14) Claims 10, 11, 19-24, 27 and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (US 6,221,840) in view of Le Page *et al.* (US 6,221,648) or Steidler *et al.* (US 6,605,286), Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993, already of record) (Wells *et al.*, June, 1993) and Tran *et al.* (*Gut* 44: 636-642, May 1999).

It is noted that the recited TEF1 is synonymous with pS2. See lines 1 and 2 on page 2 of the specification.

Claims 2, 7 and 16 patented by Podolsky ('840) are drawn to a method of treating lesions in the intestine of a patient by orally administering to the patient an intestinal trefoil factor (ITF) polypeptide, a biologically active fragment thereof, or at least one trefoil peptide. The lesions are in the intestine of a patient suffering from gastritis, digestive disorder, peptide ulcer diseases, inflammatory bowel diseases, non-ulcer dyspepsia, or Crohn's disease. The treatment of lesions includes inhibition f the formation of lesions or promotion of healing of lesions. See abstract; claims 2 and 7; and column 2; second full paragraph and lines 46-49 in column 5; and lines 44 and 45 in column 16). The administration of the peptide is by oral administration in the form of a solution, tablet, capsule or pill that the patient swallows. The peptide-containing solution can also be administered as a gastric lavage (see the section 'Use' in columns 15 and 16). The trefoil polypeptide used for treating or inhibiting the formation of lesions is PS2 (i.e., TEF1) or fragments (i.e., peptides) thereof and is produced by recombinant techniques (see claims and lines 33-60 in column 5). Podolsky ('840) expressly taught that since trefoil peptides are 'not degraded within the digestive tract', the route of administration is oral and the dosage ranges from 1 to 500 mg (see lines 42-45 in column 15). Podolsky ('840) further taught the ITF peptide is 'resistant to degradation in the digestive system' (see lines 28-30 in column 16).

Podolsky ('840) do not teach that the trefoil peptide was administered via a recombinant microorganism, or a Gram positive bacterium, such as, a *Lactobacillus* species, expressing *in vivo*, a trefoil peptide, such as, pS2 or TEF1.

However, the delivery of a therapeutically significant polypeptide via *Lactobacteria* expressing the polypeptide was well known in the art at the time of the invention as taught by Le Page *et al.* ('648), Wells *et al.* (June, 1993) or Steidler *et al.* ('286).

Le Page *et al.* ('648) demonstrated the use of a food-grade organism, *Lactococcus lactis*, for the recombinant expression and delivery of a variety of heterologous peptides, polypeptides, or proteins of diverse origin s medicaments. The recombinant product in biologically active form is delivered *in vivo* by parenteral, oral route. The *Lactococcus lactis* comprises a recombinant vector containing the coding sequence of the polypeptide or peptide desired to be expressed and delivered under the control of an inducible promoter sequence and a secretory signal sequence (see abstract; claims; Experiment 3; last full paragraph in column 4; paragraph bridging columns 4 and 5; and lines 61 and 62 in column 18). The *Lactococcus lactis* expressing heterologous protein or

polypeptide is used in the production of a useful response in a subject (see first full paragraph in column 1). The polypeptide expressed and contained intracellularly in *Lactococcus lactis* is in a biologically active conformation capable of giving the protective effect (see lines 28-30 in column 19). The oral administration ensures that the expression product reaches the appropriate location in a biologically active configuration (see lines 1-8 and 16-29 in column 21). It is taught that the use of a non-invasive microorganism to express a range of foreign proteins opens the way to the concurrent delivery of antigens and cytokines which might be used to drive a response in a desired direction (see column 2, lines 19-23).

Wells *et al.* (June, 1993) demonstrated for the first time that a heterologous peptide antigen of medical importance could be successfully expressed in substantial quantities and in a soluble form via the expression system of a food grade bacterium, *Lactococcus lactis* and be presented to the immune system in an immunogenic form (see abstract; and page 1155). Wells *et al.* (June, 1993) taught that the resultant recombinant *Lactococcus lactis* expressing substantial quantities of the heterologous peptide successfully immunized mice against lethal challenge. Wells *et al.* (June, 1993) expressly taught the continuing need in the art to develop safer vaccines and a growing interest in using live recombinant bacteria as vaccine antigen delivery vehicles which may be taken by mouth (see page 1155, left column; and page 1157, right column). Wells *et al.* (June, 1993) taught how to preload the non-commensal bacterium, *Lactococcus lactis*, with an antigen for use as an antigen delivery vector (see page 1155, right column). The recombinant *Lactococcus lactis* contains the heterologous protein gene under the control of a suitable promoter sequence and the expression vector (see page 1155, right column; and page 1157).

Similarly, Steidler *et al.* ('286) disclosed the recombinant production of a non-invasive, food grade *Lactobacillus* species for expressing or delivering one or more biologically active polypeptide antigens *in vivo* (see claims; Summary of the invention; columns 4-8; and Examples). The recombinant *Lactobacterium* can be used to deliver a range of biologically active polypeptides (see last full paragraph in column 8; and paragraph bridging columns 8 and 9). The specific bacterium species used in *Lactococcus lactis* (see last paragraph in column 13). The biologically active polypeptide can be a receptor for biologically active polypeptides (see bottom of column 5), or any peptide or polypeptide having pharmaceutical use (see first full paragraph in column 11). Steidler *et*

al. taught the broad applicability for the delivery of polypeptides via *Lactocobcteria* which are able to sustain their biological activity on a mucous membrane for a sufficient length of time to deliver a biologically active dose of recombinant cytokines and thereby augmenting an immune response to a heterologous antigen (see first full paragraph in column 4). The *Lactobacterium* comprises a recombinant vector comprising the polypeptide-encoding sequence under the control of a promoter sequence and a secretory signal sequence (see column 6). The administration of the bacterium is by oral route (see third full paragraph in column 10). Most importantly, Steidler *et al.* taught the unexpected or surprising property of the recombinant bacterium expressing or delivering the heterologous antigen. Steidler taught that given that on the mucosal membrane *in vivo*, the bacteria are in an environment which would not be expected to support their growth or viability, their recombinant *Lactobacteria* were surprisingly able to deliver a polypeptide in an amount or dose sufficient for the biological activity of the polypeptide to results in biological effect (see lines 1-7 in column 9). The biological effect is therapeutic effect beneficial to the individual to whom it is administered including amelioration of at least one symptom (see fourth full paragraph in column 10).

In an established model of colitis which exhibits damage and repair profiles in common with the human inflammatory bowel diseases, ulcerative colitis and Crohn's disease, Tran *et al.* expressly demonstrated that exogenously administered trefoil peptide induces the therapeutic effects comprising promotion of rapid repair of the epithelium and reduction in inflammatory indexes. Tran *et al.* taught that the trefoil peptides reduce the symptoms of colitis by multiple mechanisms (see title; abstract; paragraph bridging left and right columns on page 641; and right column on page 641).

Given the demonstrated therapeutic effects of exogenously administered trefoil peptides in diseases including ulcerative colitis and Crohn's disease in an art accepted model of colitis as taught by Tran *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Podolsky's ('840) therapeutic pS2 or TEF1 trefoil peptide recombinantly in Le Page's ('648), Wells' (June 1993) or Steidler's ('286) *Lactobacillus lactis* using Wells' (June, 1993), La Page's ('648) or Steidler's ('286) expression and delivery method to produce the instant invention, with a reasonable expectation of success, because Wells *et al.* (June, 1993) taught that a heterologous peptide antigen of medical importance could be successfully

expressed in substantial quantities and in a soluble form via *Lactococcus lactis* which can be taken by mouth and be presented to the immune system in an immunogenic form. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing Podolsky's ('840) pS2 trefoil peptide, having a demonstrated therapeutic effect against Crohn's disease, in Wells' (June, 1993), La Page's ('648) or Steidler's ('286) *Lactobacillus lactis* such that a substantial quantity of soluble pS2 can be expressed *in vivo* for driving a useful response in a desired direction as taught by La Page *et al.*

Claims 10, 11, 19-24, 27 and 29 are *prima facie* obvious over the prior art of record.

15) Claim 26 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (US 6,221,840) as modified by Le Page *et al.* (US 6,221,648) or Steidler *et al.* (US 6,605,286) or Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993, already of record) (Wells *et al.*, June, 1993) and Tran *et al.* (*Gut* 44: 636-642, May 1999) as applied to claim 10, and further in view of Silk (WO 82/03329, already of record).

The teachings of Podolsky ('840) as modified by Le Page *et al.* ('648), Wells *et al.* (June, 1993), or Steidler *et al.* ('286) and Tran *et al.* are explained above, which do not teach the use of a gastric catheter for the oral administration of their recombinant microorganism.

However, the use of a gastric catheter as an alternative to the oral administration of a therapeutic composition, especially in patients who are incapable of feeding themselves was routine and conventional in the art at the time of the invention. For instance, see the abstract of Silk.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Silk's gastric catheter to deliver Podolsky's ('840) therapeutic composition as modified by Le Page *et al.* ('648), Wells *et al.* (June, 1993), or Steidler *et al.* ('286) and Tran *et al.* to produce the instant invention, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing an alternative means of oral administration especially in those patients who are incapable of feeding themselves as taught by Silk.

Claim 26 is *prima facie* obvious over the prior art of record.

Remarks

16) Claims 10, 11, 19-24 and 26-29 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (703) 872-9306.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

July, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER